Tetrahedron. Vol 25, pp 4331 to 4337. Pergamon Press 1969 Printed in Great Britain

MECHANISM OF PYRIDYNE FORMATION FROM HALOPYRIDINES[1]

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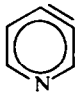
(*Received in USA* 2 *January* 1969; *Received in the UK for publication* 13 *May* 1969)

Abstract—Rates of hydrogen-deuterium exchange of 3-chloro- and 3,5-dichloropyridine in MeOD–MeONa were studied. Deuterodeprotonation of 3-chloropyridine at 110·2° is 53 times faster at H-4 than at H-2. At 75° the value of the *ortho* chloro rate factor for exchange is 800; the *para* nitrogen rate factor is 3000. Interrupted dehydrohalogenation of 3-chloropyridine-2 or 4-*d* and 3-iodopyridine-4-*d* in NH_3–$NaNH_2$ to give 3,4-pyridyne results in no detectable loss of label at 2 in the chloropyridine but reduction and enrichment of 4-*d* in the chloro and iodo compounds, respectively. Results are interpreted in terms of the reactions of halopyridyl anions.

INTRODUCTION

HALOPYRIDINES and fused ring halopyridines may undergo dehydrohalogenation by strong bases to give heterocyclic arynes or hetarynes. When the halogen is *meta* to the annular N atom and dehydrohalogenation may take place by removal of hydrogen either *ortho* or *para* to the nitrogen, elimination takes place solely by loss of the *para* hydrogen. Thus, 3,4-pyridyne (I) but not 2,3-pyridyne (II) forms as an intermediate during dehydrohalogenation of 3-halopyridines.[3]



I

II

We present the results of studies designed to indicate the relative acidities of positions adjacent to halogen in 3-halopyridines. Investigations involve H–D exchange in methanol under conditions which do not lead to 3,4-pyridyne as well as in ammonia where this intermediate is formed.[4]

RESULTS

Kinetic data on the methoxide ion catalyzed proteodedeuteration of 3-chloropyridine and deuterodeprotonation of 3-chloro- and 3,5-dichloropyridine in methanol are given in Table 1.

Rate constants, obtained by standard NMR methods,[5,6] indicate that H-4 of 3-chloropyridine exchanges 53 times faster than H-2 at 110·2°. Positions 2 and 5 in this molecule have about the same kinetic acidity and exchange was not detected at position 6 under these conditions. Methoxydechlorination did not compete with hydrogen exchange; the rate constant (extrapolated) for this reaction at 110° is $3{\cdot}4 \times 10^{-8}\ M^{-1}\ sec^{-1}$.[7]

The most acidic site in 3-iodopyridine is H-4 and the 4 position in 3,5-dichloropyridine undergoes hydrogen exchange more rapidly than the 2,6 positions.

TABLE 1. RATE CONSTANTS FOR HYDROGEN-DEUTERIUM EXCHANGE OF 3-CHLORO- AND 3,5-DICHLOROPYRIDINE IN METHANOL

Pyridine[a]	Position[b]	T, °C[c]	[NaOMe][d] M	$10^6 k$[e] M^{-1} sec^{-1}
3-Chloro	4-D[f]	74·2	1·71	3·57
	4-D	78·0	1·25	4·95
	4-D	78·0	1·42	3·67
	4-D	100·8	0·83	44·6
	4-H	110·2	1·17	204·0
	2-H	110·2	1·17	3·86
	5-H	110·2	1·17	4·69
3,5-Dichloro	4-H	75·1	0·047	598·0
	4-H	75·1	0·072	652·0
	4-H	75·1	0·094	603·0
	4-H	75·1	0·096	686·0
				Avg. 635·0 ± 42

[a] 0·5–1·0 M; [b] D indicates exchange in MeOH; H indicates exchange in MeOD. [c] ±0·2°; [d] Corrected for thermal expansion; [e] k exp/[NaOMe]; [f] E_{act} = 25·2 kcal/m, ΔS^* (75°) = −13 eu.

Comparison of the rate constant for deuterodeprotonation with that (extrapolated) for proteodedeuteration of 3-chloropyridine at 110° indicates that the rate constant for reaction in MeOD is 2·0 times larger.* A ratio of 2·3 was found for exchange rates of pentafluorobenzene in MeOD and MeOH at 40°.[8]

A partial rate factor for an *ortho* chloro substituent may be obtained by dividing the second order rate constant for exchange at H-4 of 3,5-dichloropyridine by a similar constant for exchange at D-4 of 3-chloropyridine-4-*d*, provided the above isotope correction factor of 2·0 is employed. The value 0·8 × 10^3 for the *ortho* chloro rate factor at 75° is to be compared with the value 1·9 × 10^3 at 50° obtained in a similar manner from rates of exchange of deuterated chloropyridine N-oxides in MeOH.[5,†]

Similarly, comparison of the exchange rate constant for H-4 of 3,5-dichloropyridine with the extrapolated rate constant for proteodedeuteration of 1,3-dichlorobenzene-2-*d* in MeOH[9] gives a *para* annular nitrogen rate factor. The value 3·0 × 10^3 for this factor at 75° is similar to the value 10^4 obtained from a comparison of rates of exchange at the 4-position of pyridine with those of benzene in ND_3—$NaND_2$ at −25°.[10]

Information about pyridyne formation was obtained from studies of D–H exchange in specifically deuterated 3-halopyridines under dehydrohalogenation conditions. 3-Chloropyridine-2 or 4-*d* and 3-iodopyridine-4-*d* were partially dehydrohalogenated in $NaNH_2$—NH_3.

* Under these conditions internal return is likely. There should be essentially no kinetic isotope effect for hydrogen transfer.[8] The rate factor is primarily the result of a solvent isotope effect.

† The uncertainty in the chloro rate factor obtained from H–D exchange of the N-oxides is about a factor of 2.

Three distinctly different results were obtained from these reactions. The data in Table 2 show that the deuterium content of 3-chloropyridine-2-*d* does not change measurably under conditions which lead to the formation of 3,4-pyridyne. However, as this pyridyne is being generated reduction in the deuterium content of 3-chloropyridine-4-*d* does take place and by contrast, enrichment in the deuterium content of 3-iodopyridine-4-*d* occurs. While no kinetic isotope effect is discernible for the chloro compounds the reaction of 3-iodopyridine to form 3,4-pyridyne proceeds with an apparent kinetic isotope effect k_{-H}/k_{-D} of 2·6.*

TABLE 2. INTERRUPTED DEHYDROHALOGENATION OF 3-HALOPYRIDINES-*d* WITH $NaNH_2$ IN BOILING AMMONIA

Pyridine	% Deuterium[a] Initial	final	% Halide Ion formed	k_{-H}/k_{-D}
3-Chloro-4-*d*[b]	75	20	46	—
3-Chloro-2-*d*[b]	61	61	30	—
3-Iodo-4-*d*	30	43	49	2·9
3-Iodo-4-*d*	29	44	60	2·3

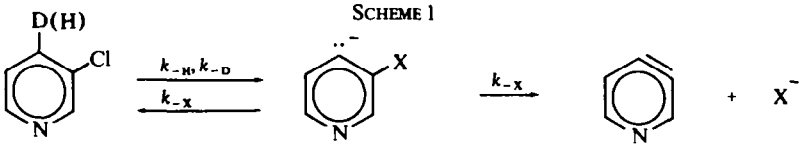
[a] ±5% [b] Data taken from Ref 4.

The reactions in ammonia are relatively fast and the time for the addition of halopyridine constitutes a portion of the reaction time. In the case of 3-iodopyridine, for example, this serves to decrease the magnitude of the apparent isotope effect. Such complications have no bearing on our main conclusions, however.

DISCUSSION

The mechanism of formation of 3,4-pyridyne from 3-halopyridines is likely to be similar to that for the formation of arynes under the same conditions.[3c] As with aryl halides, it is probable that the pyridyl halides are deprotonated by base to give halopyridyl anions which then eliminate halide ion, Scheme 1.

SCHEME 1



Several facts support this contention: (1) Base-catalyzed deprotonation to give carbanionic intermediates is not an uncommon reaction of heteroaromatic compounds. Pyridine N-oxides and N-methylpyridinium ion undergo such deprotonation reactions.[12] (2) The *ortho* chloro rate factor obtained from the rates of hydrogen exchange of chloropyridine N-oxides[5] favorably compares with that obtained from chloropyridines. It is unlikely that similar values would be obtained for this factor if different

* Data were treated according to the method developed.[11]

types of intermediates were formed in the N-oxide and pyridine series. (3) The magnitude of the apparent kinetic hydrogen isotope effect in the reaction of pyridyl halides increases with increasing atomic number of the halogen leaving group. The reactions of aryl halides to give arynes show a similar effect.[11]

The results of the interrupted dehydrohalogenation reactions of deuterated 3-halopyridines in ammonia are understandable in terms of the reactions of halopyridyl anions. Reaction of a 3-halo-4-pyridyl anion with solvent gives unlabelled 3-halopyridine and loss of halide ion from the anion results in the formation of 3,4-pyridyne, Scheme 1. The degree of change in the isotopic content of starting material depends on two ratios, the isotope effect $k_{-H}/k_{-D} = i$ and the partitioning of anion to halopyridine and to 3,4-pyridyne, k_H/k_{-X}. Thus, when there is an isotope effect, proteo reacts faster than deutero substrate. This in itself would lead to an increase in the amount of D relative to the amount of H isotope in substrate. But opposing this enrichment is the formation of proteo halopyridine from a reaction of anion with solvent, since anion formed from either H or D starting material gives only H substrate. Therefore, a value of k_H/k_{-X} cannot be specified without a knowledge of the magnitude of i. This means that from an experimentally determined change in the H–D ratio of substrate a range of values of k_H/k_{-X} may be computed. As larger values of i are employed in the computations, larger values of k_H/k_{-X} are generated.*

With this limitation in mind and the knowledge that 3-halopyridines do not form detectable quantities of 2,3-pyridyne in ammonia[3] an explanation of the results of the interrupted elimination reactions can be given. The following assumes that i has the value $\leqslant 6$. For 3-chloropyridine-4-*d* reduction in the D content of starting material results because the rate of reaction of 3-chloro-4-pyridyl anion with solvent exceeds that for chloride ion loss, $k_H/k_{-Cl} > 1$. For 3-iodopyridine-4-*d* enrichment in D content results because the rate of reaction of 3-iodo-4-pyridyl anion with solvent is similar to or less than the rate of iodide ion expulsion. No measurable change in D content of 3-chloropyridine-2-*d* is observed because detectable amounts of the 3-chloro-2-pyridyl anion do not form.

Because protonation of the 3-iodo-4-pyridyl anion prior to iodide ion loss is not taken into consideration in calculating the kinetic hydrogen isotope effect, reported values in Table 2 are apparent values only.[11] The true magnitude of this isotope effect, k_H/k_{-D}, ought to be larger.

The results of the hydrogen exchange experiments in methanol and in ammonia indicate that the 4 position of 3-halopyridines is more acidic than the 2 position. This reactivity pattern suggests that the mechanism of hydrogen exchange is similar for the two media. In MeOD, however, the halopyridyl anion undergoes deuteron capture at a much greater rate than its suffers halide ion loss, $k_D/k_{-X} \gg 1$. This result is largely a consequence of the fact that methanol is a much more acidic solvent than ammonia.

Because the effect of the halogen atom is expected to be the same at adjacent positions 2 and 4, the unusual positional acidity pattern of 3-halopyridines must be due to the annular nitrogen atom.

Hydrogen exchange studies on pyridine and the diazines in hydroxylic solvents

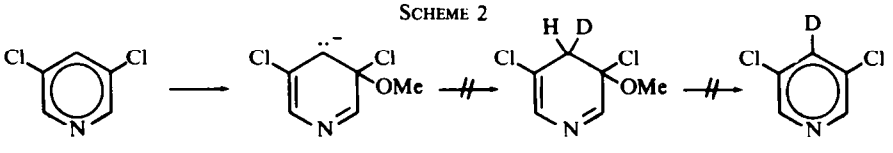
* An equation relating k_H/k_{-X}, k_{-H}/k_{-D} and the degree of change of the isotopic content of substrate has been reported.[13]

indicate that a N atom activates all positions for exchange but that positions adjacent to nitrogen are less acidic than more remote centers.[10,14,15] We suggest that two factors need to be considered in accounting for the decreased acidity of sites adjacent to nitrogen, relative to more removed centers. These are (a) electrostatic, repulsive interaction between the unshared electron pair of nitrogen and the electron pair of the anion in the transition state and in the intermediate ion and (b) the reduction in the amount of s character in the C_2H bond resulting from an enlarged internal ring bond angle.* A discussion of these factors will be presented in a future publication dealing with H–D exchange of pyridine and the diazines in MeOD.[17]

Partial rate factors provide a measure of the effect of groups on the rates of aryl anion formation. It is instructive to compare our rate factors for chlorine and nitrogen with those for fluorine. Rate factors are available for aryl fluorides in NH_3[18] and in methanol.[8] The *ortho* chloro rate factor is understandably less than the value of $1{\cdot}8 \times 10^5$ (MeOH, 40°) for the more electronegative F atom. However, the value of the *para* fluoro rate factor,[8] 14, is considerably less than that for the *para* nitrogen rate factor. The activating influence of an annular N atom on the acidity of a *para* position is especially large and is considerably larger than the influence of most *para* groups.[18] This activation is likely to be due primarily to an inductive and not to a resonance effect. Resonance effects are not likely to serve as the primary mode of stabilization of anions generated by deprotonation of annular positions in N-Methylpyridinium ion,[12] for example. The nitrogen nucleus in pyridines provides strong electrostatic stabilization of the anion developing at the *para* position.

Hydrogen exchange studies on 3,5-dichloropyridine rule out an alternate mechanism of exchange. Exchange can not take place on the adduct formed by the addition of methoxide ion to the 3 or 5 position of substrate, Scheme 2, because this would lead to methoxydechlorination along with hydrogen exchange. Chloride ion is a much better leaving group than methoxide ion and exchange is observed to be faster than methoxydechlorination.

SCHEME 2



Our results coupled with previous studies on the amination products from 3-halopyridines show that the rates of deprotonation and halide ion loss to give 3,4-pyridyne in NH_3 occur faster than deprotonation and halide ion loss to give 2,3-pyridyne.

* The NCC angle of pyridine is about 4° larger than the 120° angle in benzene.[16]

EXPERIMENTAL

Mass spectra were obtained on an Hitachi Perkin–Elmer RMU-6E spectrometer and NMR spectra were recorded using a Varian Associates A-60A instrument. 3-Chloropyridine (Aldrich Chemical Co.) was redistilled, b.p. 148–151°, prior to use. 3,5-Dichloropyridine, 2,3-dichloropyridine and 3-iodopyridine were used as obtained from Aldrich Chemical Co. D_2O containing >99% D was obtained from Columbia Organic Chemicals. Solutions of MeONa were prepared by dissolving freshly cut Na in MeOH or MeOD under N_2. Constant boiling DI was prepared from constant boiling HI and D_2O; 78% resulted after two exchanges.

3-Chloropyridine-4-d. A 5 g sample of 3-chloropyridine was heated to 74° with 2·5 g MeONa and 10 ml MeOD for 18 hr. Then, about 5 ml MeOD was allowed to distil, and 10 mj water, saturated with NaCl

was added. This soln was extracted twice with 5 ml portions ether and the ethereal extracts were dried and distilled. A yield of 3 g of 3-chloropyridine, b.p. 148–150° (60%), was obtained. Analysis by NMR showed 76% deuterium in the 4 position.

3,5-Dichloropyridine-4-d. A 3·5 g sample of 3,5-dichloropyridine was heated at 74° with 7 ml MeOD and 1 g MeONa for 48 hr. The reaction mixture was then diluted with 10 ml ether, and the mixture was washed with 10 ml water. The ethereal soln was evaporated, and the solid residue was recrystallized from aqueous MeOH. A yield of 3 g (85%) of material, m.p. 63·5–64·5° was obtained (Lit.[19] m.p. is 64–65°). Analysis by NMR showed 78% D at the 4 position, and about 2 percent at the 2,6 positions. The following mass distribution was obtained from the low voltage mass spectrum: d_0, 17·8%; d_1, 72·6%; d_2, 9·7%.

3-Chloropyridine-2-d. A mixture of 10 g 2,3-dichloropyridine and 50 ml constant boiling DI was warmed to 80°, and stirred magnetically for 18 hr. The mixture was then made strongly alkaline with 30% KOH, while being cooled in an ice bath. The alkaline soln was then extracted twice with 20 ml portions ether. The combined ethereal extracts were dried with $MgSO_4$, and distilled. A fraction, b.p. 145–155°, was redistilled to give 2 ml product, b.p. 148–150°, which was shown by its gas chromatogram to contain over 93% 3-chloropyridine (area ratio). Analysis of this sample (32% yield) by NMR showed 61% D at the 2 position; no impurities could be detected.

3-Iodopyridine-4-d. A sealed tube containing 10 g 3-iodopyidine and 10 ml 2.2M MeON in MeOD was incubated at 100° for about 2700 min. The contents then were added to 50 ml 30% KOH and the mixture was extracted twice with 25 ml ether. The dried ($MgSO_4$) extracts were concentrated and the residue sublimed at 0·5 torr with an apparatus which was cooled by MeOH circulated through a Dry Ice-isopropanol heat exchanger. The collected solid was then resublimed to give 7·8 g 3-iodopyridine (78%), m.p. 50–52°. This solid was analyzed by NMR in CCl_4 soln, and was found to contain 66% 4-*d*, the 5,6 protons serving as internal standard. Mass spectral analysis showed: d_0, 28·3%; d_1, 63·2%; d_2, 8·5%. Some deuterium probably is in the 2 and/or 5 positions as well.

Kinetics of hydrogen–deuterium exchange of 3-chloropyridine in methanol. A typical de-deuteration run was prepared by adding a mixture of 0·07 ml 3-chloropyridine-4-*d*, 0·02 ml t-BuOH, 0·488 ml MeOH, and 0·418 ml 3·64 M methanolic NaOMe to a dry NMR sample tube. After a time zero NMR spectrum was made, the tube was immersed in a constant temp bath and removed periodically for NMR measurement. The integrals of proton signals were measured in four successive sweeps, and the average value was taken. Standard deviations of individual sweeps from the average ranged from ±2–5%. Sufficient time was allowed to elapse between sweeps to avoid saturation effects. The quantity log Q was plotted as a function of time. In this quantity A represents the

$$Q = \frac{(A/A_{std})_{eq} - (A/A_{std})}{(A/A_{std})_{eq} - (A/A_{std})_0}$$

area of the reacting proton signal, and A_{std} represents the area of the t-Bu proton signal. The values of the ratio A/A_{std} were experimentally determined for time zero, and points of the run. The value of the ratio at equilibrium was calculated from the amounts and deuterium contents of the reagents used. The slope of the plot of log Q versus time was determined by visually fitting the best straight line through the experimental points, numbering about five. The base concentration, as calculated from the total volume of MeONa used, was corrected for expansion using the ratio of the density of MeOH at the reaction temp to the density at room temp.[20] The pseudo-first order rate constants were divided by the corrected base concentrations to give the second order rate constants, which are given in Table 1. In proteodeuteration runs log $(-Q)$ was plotted as a function of time. Reactions were followed for 1–3 half-lives. Following exchange the base concentration of randomly selected samples was determined by titration. These values generally agreed with initial values to within 10%.

Kinetics of deuteration of 3,5-dichloropyridine in methanol-0-d. A typical run involving deuterodeprotonation at the 4 position was made by adding 0·084 g 3,5-dichloropyridine, 0·02 ml t-BuOH, and 0·093 ml 1·103 M MeONa in MeOH-0-*d* to a 1 ml volumetric flask. The flask was then made up to the mark with MeOD and the contents were transferred to a dry NMR tube. The tube was sealed, a time zero NMR spectrum was made, and the tube was immersed in a water bath thermostated at 75·1 ± 0·2°. The tube was removed periodically for analysis. The pseudo-first order and the second order rate constants were obtained in the same manner as those for 3-chloropyridine, and are given in Table 1.

Interrupted dehydrohalogenation of deuterated 3-halopyridines. The procedure is the same for 3-chloropyridine-2 or 3-*d* and for 3-iodopyridine-4-*d*. The method is described for the first substrate.

About 200 ml ammonia was condensed into a flame-dried N_2 swept flask fitted with Dry Ice condenser. A total of 0·54 freshly cut Na metal was added in small portions, and a small crystal of ferric nitrate was added to catalyze amide formation. When all the Na had been converted to $NaNH_2$, as evidenced by the disappearance of the blue coloration, 2 g 3-chloropyridine-2-*d*, with 61 – 5% deuterium content, in 10 ml anhyd ether was added over a 1 min interval. The mixture was allowed to stir for three additional min, then the reaction was quenched by the addition of 4 g solid NH_4NO_3. The liquid ammonia was allowed to evaporate overnight. The residue was diluted with about 15 ml water, and extracted twice with 5 ml portions ether. The aqueous layer was quantitatively saved. The combined ethereal extracts were dried with $MgSO_4$, and distilled. Redistillation gave about 1 g 3-chloropyridine, b.p. 148–150°. This sample was found to be homogeneous by gas chromatography, and NMR analysis showed 61 – 5% deuterium content.

The volume of the aqueous extract was reduced to about 20 ml, acidified with HNO_3, and then diluted to 25 ml. An argentometric titration of aliquots with $AgNO_3$ showed that 80% of total chlorine present in the original starting material had been liberated as chloride ion.

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Note added in proof: Calculations using the extended Hückel theory (EHT) indicate the 4-pyridyl anion is 1·9 kcal/m (0·08 eV) more stable than the 2-pyridyl anion. The 53-fold spread in H-D exchange reactivity found for the 4 and 2 positions of 3-chloropyridine corresponds to a $\Delta\Delta G^{\ddagger}$ of 3·0 kcal/m. EHT results suggest that nitrogen lone pair destabilization of adjacent electron pairs is a dominant effect. W. Adam, A. Grimison and R. Hoffmann, *J. Am. Chem. Soc.* **91**, 2590 (1969).